I. Scientific Abstract

It is estimated that prostate cancer in the United States will be the leading male cancer diagnosis and the second most common cause of male cancer death in 1998. For patients diagnosed with prostate cancer, 10-15% of patients will have metastatic cancer at the time of diagnosis. Of patients undergoing radical prostatectomy, approximately 20-30% will have positive margins or capsular penetration at the time of their resection. Thus, a significant number of patients are at risk for post-surgical local recurrence. Additional patients will develop metastatic prostate cancer after some form of definitive initial therapy (either surgery or radiation). The most common anatomical locations for metastatic disease are bone and lymph nodes. Androgen ablation can delay progression at this time, but no effective therapy is available for these groups of patients and the need for new therapeutic approaches to treat advanced prostate cancer is clear.

Direct introduction of therapeutic genes into malignant cells *in vivo* may provide effective treatment of solid tumors, such as adenocarcinoma of the prostate. The trial proposed will use a form of therapeutic gene therapy based on the thymidine kinase gene expression under the transcription regulation of the osteocalcin (OC) promoter and activated by the prodrug valacyclovir. The OC promoter functions primarily in osteoblasts found in growing bone. Additionally, it has the ability to drive gene expression in a series of tumors that can undergo ossification. With a majority of its metastatic lesions demonstrating an osteoblastic nature, prostate cancer cell lines expresses high levels of thymidine kinase(TK) activity after infection with the adenovirus containing the osteocalcin promoter driving hsv-TK (Ad-OC-TK). Several non-prostate cancer cells and normal cells examined failed to demonstrate TK activity after infection with Ad-OC-TK. When cell lines and animals containing human prostate cancer are infected with Ad-OC-TK and exposed to ACV, there is a marked diminution in tumor growth, both *in vitro* and *in vivo* . Therefore, by using a tissue-specific promoter to drive a suicide gene that requires cell division for death, this gene therapy approach doubly protects normal mammalian cells and may allow for systemic delivery of this gene therapy by increasing the therapeutic window.

The protocol describes a dose escalating (5×10^8 pfu to 5×10^{10} pfu) Phase I trial to treat patients with recurrence of prostate cancer after surgical resection or metastatic prostate cancer. In the case of patients with post-surgical recurrence of prostate cancer, the site of recurrence, which is measurable by radiological evaluation, will be injected under transrectal ultrasound or CT-guided imaging with the Ad-OC-TK. The group of patients with metastatic index lesion will be injected by interventional radiology with the guidance of either CT or plain radiographs dependent on location. One index lesion will receive two injections of the virus separated by one week and the patient will receive three weeks of valacyclovir from the time of the first injection. This treatment will be limited to one lesion per patient, so patients with multiple lesions will have one index lesion treated. The patients will be assessed for safety of this protocol, but serologic, tissue and radiologic evidence will be examined to confirm the biologic feasibility and the potential efficacy of this approach.